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3D Printing Technology in Pharmaceuticals and Biomedical: A Review

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ABSTRACT

3D printing is also known as additive manufacturing, which is the potential way to transform the manufacturing as well formulation in pharmaceuticals and biomedical industries. Three-dimensional (3D) Printed medicines are revolutionsing the pharmaceutical market as potential tools to achieve personalized treatments adapted to the specific requirements of each patient, taking into account their age, weight, comorbidities, pharmacogenetic, and pharmacokinetic characteristics. Additive manufacturing or 3D printing has wide range of techniques which are classified in many categories but most commonly used in the 3D printing of medicines are: printing-based inkjet systems, nozzle-based deposition systems, and laser-based writing systems, in addition to both polymer filaments and hydrogels as materials for drug carriers.

Keywords: 3D printing, Additive Manufacturing, Bioprinting, Drug delivery, Medical devices

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INTRODUCTION

There is always focus towards new concepts in drug design, better understanding of material properties, manufacturing technology and processes that will assures high quality of dosage forms. Within last few decades the patient-centric drug product development has been taken under considerable attention. The focused on novel dosage forms and technological processes has increased. Three dimensional printing (3DP) is believed to be the most revolutionary and powerful technique for the development of novel drug delivery system. This technique is versatile tool of precise manufacturing of various devices. It helps in serving as a technology tool for developing novel dosage forms, tissues and organs engineering as well as disease modeling.

Nowadays, three-dimensional printing is one of the fastest developing branches of technology, art and science, and still broadens the applications. The term three-dimensional printing or 3D printing defined by International Standard Organization (ISO) as: fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology. In contrast to commonly used subtractive and formative manufacturing methodologies, this technique is one of the methods of additive manufacturing (AM) in which the parts are prepared from 3D model data in the process of joining materials layer by layer. The practical approach of AM is called rapid prototyping (RP) and its advantages include the reduction of prototyping time and costs, easy modifications of a product at a designed level, the possibility of manufacturing of small objects, individualized product series or structures impossible to be formed with subtractive techniques. The novel approaches in the formulation of solid dosage forms for personalized as well as individualized therapy are particularly focused; however TDDS as well as biomedical applications of additive manufacturing technique including implants, surgical models, bioprinted materials and biorobotics is also mentioned.[1, 2]

Pharmaceutical potentials of 3D printing

The processes that are traditionally adopted by pharmaceutical industries such as milling, mixing, granulation and compression sometimes results in uneven qualities of the final products depending on the factors such as drug loading, drug release, drug stability and pharmaceutical dosage form stability. On the other hand, 3D printing, as a powerful tool technology, has competitive advantages such as improved R and D productivity, improved safety, efficacy and accessibility of medicine. The major advantages of 3D printing that makes it much more attracting are:

1. Personalization

The current popularity of 3D printing in various fields is often described as a new industrial revolution. While in the last centuries industries were focused on mass-manufacturing, automation and standardization in order to reduce costs and increase profit, with the advent of 3D printing they are shifting to on-demand production of either a small number of objects or even one object at a time (small batches), possibly customized, at affordable prices. Products characterized by complex geometries can also be fabricated and real-time modified to meet individual needs at little or no extra costs. 3D printing is spreading throughout all manufacturing stages of production, from the prototyping step to the fabrication of consumer products. By shortening the design, manufacturing and production cycle, thus simplifying the manufacturing chain, this new technology has brought the site of object fabrication closer to that of demand. Moreover, it has proved effective as a rapid prototyping tool useful to evaluate the form, fit and function of many objects before their production on a large scale.

- Personalized medicine: Personalized medicine generally consists in tailoring medical treatments to the characteristics, needs and preferences of each single patient, and it involves purposely run diagnosis, therapy and follow-up. The concept could be extended to include pre-emptive medicine aimed at reducing the risk of diseases a subject has shown susceptible to, by changing his lifestyle, diet and habits and by advising him on the use of peculiar supplements or drugs.

- Personalized therapy: In the medical field, 3D printing was initially employed by surgeons as an aid in creating 3D models of patients to better visualize their anatomy, particularly in the case of individuals with unique structures or anomalies, which would require complex surgeries. This technique has partially replaced more established ones (e.g. solvent casting and particulate leaching, membrane lamination, molding) since it enables fabrication, starting from biocompatible materials, of items perfectly fitting the anatomical characteristics of the patient as highlighted by diagnostic imaging tools (e.g. X-ray, computed tomography, nuclear magnetic resonance). Scaffolds are intended for different functions, such as space filling, 3D structures that organize proliferating cells into a desired tissue, in situ vehicles for the delivery of active molecules (e.g. antibiotic or anti-inflammatory drugs, growth factors).

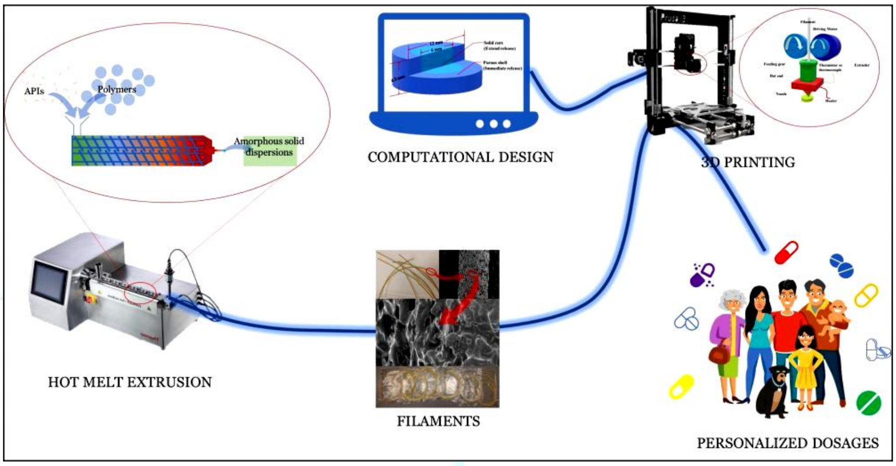

Figure 1: Personalized Dosage through Additive Manufacturing

2. Tailored medication

3D printing helps in the production of medication as per the required needs of the patients or depending upon the medication required. The method can be adopted in case of pediatrics dose, where the range of dose may vary. Similarly, the shape of the dosage form can be altered for the patients with swallowing difficulties. 3DP is highly flexible and simple method to change the shape and size of the dosage form.

3. Create complex shapes

3DP allows the formations of complex shapes and that too with accurate dose of medication or active pharmaceutical ingredients, even as low as 10-12 mole per tablets which helps in reducing the side effects which are observed due to excessive doses. As compared to conventional methods where complex geometries were not possible it can be achieved easily by 3D printing. Similarly, different shapes and sizes also results in different release profile. Complex shapes results in modified release, adjust drug loading and mask the taste of the medication.

4. Sustained release

Drug release can be easily controlled and targeted by 3D printing. It can be adopted by printing a binder in the layers of the matrix powder. This creates a barrier between the layers of API and allows variation in release profile.

5. Unique dosage form

In pharmaceutical production process, 3D printing can be used to create unique and limitless dosage forms. 3DP is used to create novel dosage forms.

6. Mini dispenser unit

The set up for 3D printers require minimal space allowing them to fit in any environment, are cost effective. 3D printing is a computer aided design that means it can be controlled using computer software and network. Moreover, 3D printing technologies allows individualization of medication. These characteristics allows 3D printer to function as a mini-dispenser to potentially bring tablet manufacturing closer to patients.

7. Integrated with Health Care Network

Physicians and pharmacists can modify the next dose or drug combinations according to patient's need. As 3D printers are remotely controlled, 3D printing can became easily accessible to the patients. Hence, this improves the patients' compliance and shortens the time of clinical response to patient's needs.

8. Accelerated Disintegration

3D printing makes a huge difference with powder compression in terms of disintegration process. The pattern of powder aggregation is different in both the conventional and newer method. In 3D printing powder binding strength is higher in the periphery and lowers in the centre which leads to rapid disintegration of tablets. Aprecia's Zip Dose® has found to disintegrate in less than 10s whilst containing a high dose of piracetam (1000 mg).

9. Tool Less

3DP can eliminate the need for tool production and therefore, reduced cost, lead time and labour associated with it.

10. Sustainable/eco friendly

3D printing being a new and emerging technology is energy-efficient and provides environmental efficiencies. It utilises up to 90% of standard materials, and, therefore, creates less waste. It has stronger design that imposes a reduced carbon footprint compared with traditionally manufactured products.

11. Short production time

3D printers are time efficient which shortens the product development design cycles.

12. Manufacturing process

The manufacturing process is quite easier and cost effective. The time of processing is less due to improved tools, less waste and takes fewer steps to assemble the setup and also reduce lead time via functional integration of parts.

13. Engineering and Maintenance

3D printers have more flexible set up and maintenance processes. It is cost-efficient industrial engineering.

14. Logistic

3D printing is promising tool whereby products can be manufactured on demand and place where needed which reduces the inventory and logistics handling and moreover the transportation and related costs. [3, 5]

USA-FDA approved 3D printed drug products: Worldwide

Aprecia Pharmaceuticals in August 2015 introduced the first drug product using the ZipDose technique for the treatment of epilepsy. FDA approved the drug product SPRITAM levetiracetam for oral use for the treatment of partial seizures, primary generalized tonic clonic seizures, myoclonic seizures in adults and children. Spritam was formulated by ZipDose technology that produced a porous formulation that disintegrates rapidly. Spritam was designed to fill the needs of the patients who have problems with the current medication therapy. ZipDose technology enables the incorporation of large doses up to 1000 mg in single dosage form. This technology enhanced the patient compliance by easy administration of drug. ZipDose technology combines the drug formulation science with unique manufacturing capabilities of 3D printing. Aprecia pharmaceuticals have the FDA approved licence for developing the pharmaceutical dosage form worldwide. [5, 6]

Table: Fabrication of dosage forms by 3D printing technology

3D printing	**Dosage form**	**Drug**
FDM	Catheter	Nitrofurantoin
FDM	Implant CR	Dye
FDM	General Device	Gentamicin sulphate, Methotrexate
FDM	Implant	Nitrofurantoin, Hydroxyapatite
Thermal Inkjet printer	Tablet	Prednisolone
Inkjet Printing	Implant	Levofloxacin
Thermal inkjet printer	Solution	Salbutamol
Inkjet printing	nanoparticles	Rifampicin
Thermal inkjet printer	Solid dispersion	Felodipine
Thermal inkjet printer	Nano suspension	Folic acid
Desktop 3D printer	Tablet	Guaifenesin
A lab-scale 3DP machine	Capsule	Pseudoephedrine HCl
3DP	Tablet	Acetaminophen
3DP	Multi-drug implant	Rifampicin, Isoniazid
Extrusion printing	Tablet	Captopril, Nifedipine, Glipizide
3D printer	Microfluidic pump	Saline solution
3D printer	Fast-disintegrating	Paracetamol
Stereolithography 3DP	Tablets (MR)	Paracetamol
3D printer	Biodegradable patch	5-Fluorouracil
Stereolithography printer	Anti-acne patch	Salicylic acid
3D printer	Tablets	Paracetamol
Piezoelectric inkjet printer	Microparticles	Paclitaxel

CR-controlled release, IR-immediate release, MR-modified release, ER-extended release, IU-Intrauterine, SC-Subcutaneous

3D Printing Glossary: [7, 8]

- Additive Manufacturing: it is the process of joining materials to fabricate or design objects from 3D model data, generally layer by layer.
- Computer-Aided Design: it involves the use of computer systems to assist in the creation, modification or optimization of 3D drawings for particular drug products.
- Extrusion: 3D printing process which involves layer by layer deposition of molten/softened or liquid/semisolid materials through a syringe or a nozzle
- Fused Deposition Modeling: 3D printing technique that involves the use of one or more filaments, generally based on a thermoplastic material, which are extruded and deposited in a molten/softened state layer by layer
- Rapid Prototyping: production of a prototype/scale model of a physical object/assembly using 3D computer-aided design data

- Resolution: Degree of conformity of a 3D printed object to the electronic model by which it was generated
- Solidification of Powder: 3D printing technique that involves the distribution of thin layers of powder selectively joined by using drops of a liquid binder
- Stereolitography: 3D printing technique that involves the use of a UV laser to cure a photo-reactive resin, contained in a vat, layer by layer into a solid object.
- .stl FILE: file generated by a computer-aided design program that contains all the data describing the layout of a 3D object and it is the most commonly used file format for 3D printing
- Subtractive Manufacturing: process in which 3D objects are fabricated by successively cutting material away from a solid block of the latter.

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